PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 08 FEB 2005
WIPO PCT

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
633		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK 03/00718	23.10.2003	23.10.2002
International Patent Classification (IPC) or both national classification and IPC		
C07C401/00		
Applicant		
LEO PHARMA A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.05.2004	04.02.2005
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00718

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-57 as originally filed

Claims, Numbers

1-23 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18-21

because:

☒ the said international application, or the said claims Nos. 18-21 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-17, 22, 23
	No:	Claims	18-21 ?

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 18-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application according to claims 1 to 23 concerns vitamin D derivatives of general formula (I) which are said to have reduced calcemic effect while retaining a suppressive effect on the secretion of the parathyroid hormone (PTH).
In that context it is noted that the compounds of general formula (I) according to claim 1 are understood as compounds with X is a bond, a double or a triple bond (see further remarks a.).

D1 : Tetrahedron Lett., 1107-1108, 13, 1977
D2 : WO 95/02577
D3 : WO 91/00855

novelty

The subject-matter according to claims 1 to 23 is novel (Art. 33(2) PCT).

None of the documents of the available prior art discloses vitamin D derivatives which are embraced by the general formula (I) as claimed. Thus, novelty of the subject-matter claimed is given.

inventive step

The subject-matter according to claims 1 to 23 seems not to be based on an inventive step (Art. 33(3) PCT).

Structurally close vitamin D derivatives with a conjugated diene/triene moiety in the side chain are already known from eg D2 and D3 (see the present page 2). These vitamin D derivatives are said to be suitable for treating diseases characterised by abnormal cell

differentiation and/or cell proliferation, cancer, acne etc and because of their low calcemic effects particularly useful for treating hyperparathyroidism, in particular secondary hyperparathyroidism associated with renal failure, osteoporosis and for inducing osteogenesis (see D2, page 6, line 30 to page 7, line 19 and D3, page 6, in particular lines 9-11). The present structurally closely related vitamin D derivatives of general formula (I) bearing a conjugated diene/triene side chain are also useful for treating the above diseases (cf claims 18 to 20, tables A and B).

The data listed in tables A and B (see present page 11 and the letter of the appicant dated 29.9.2004) have been obtained with reference to calcitriol which does not represent the closest structural approximation which would be a comparison between the compounds known from D2 and D3 and the present ones. Thus, in the absence of the required data which show superior efficacy of the compounds claimed, ie reduced calcemic effects, it is not possible to attribute any unexpected effect to the compounds claimed and an inventive step cannot be assesssed.

industrial applicability

For the assessment of the present claims 18-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

further remarks

a. In general formula (I) according to claim 1, the definition of X representing (E,Z)-ethylene is apparently spurious and is considered to be an "ethenylene" in order to define X as the -CH=CH- bridge.

b. The term "prodrug" in claim 1 is a functional term, ie an expression attempting to define the subject-matter in terms of a desired property instead of indicating precisely the technical features which is in contrast to Art. 5 and 6 PCT.